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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/284,107	LOGTENBERG ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-10 and 13-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5-10 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 3, 5-10 and 13-18 are pending and under examination.

Specification

In view of the amendments to the specification, the objection to the disclosure is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3,5-10 and 13-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A). The as-filed specification does not provide support for the now claimed "a set of **heterologous** oligopeptides". The as-filed specification and the instant REMARKS at page 10,

paragraph 2 recite for a ***nonoverlapping*** set of multimers. The term heterologous and nonoverlapping is not synonymous. The specification does not provide even a definition for said term, especially as used in the claimed context. The Webster's dictionary defined "heterologous" as derived from a different species. This can very well be true since a library of polypeptides can bind to different set of heterologous that can be derived from different target protein of different species. However, as stated by applicants in the REMARKS, the Example disclose a set of 25 ***nonoverlapping*** oligopeptides that span the extracellular domain of the CD64 molecule. [It is suggested that applicants use the terms in the as-filed specification.]

B). The specification fails to provide a written description for a method that identifies a polypeptide that includes the steps of synthesizing a set of heterologous oligopeptides derived from a target protein. The written description in the specification relates to specific set of 25 nonoverlapping peptides (12-mer) that spans the CD64 extracellular domain. Other than the specific embodiments in the specification, the specification does not describe any set of heterologuous oligopeptides that can be derived from any type of target. The claims do not recite for any structure or

sequence for any of the claimed variables. There is not enough description for numerous different variables in the specification with undefined structures. Because of the high specificity reaction of antibodies to antigens, the absence of any adequate written description or a single specific compound description would not suffice. A "written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials". University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405(1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993. See also, University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5-10 and 13-18, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing

to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons set forth in the last Office action.

In view of the amendments to the claims, the rejection has been overcome in part. Those rejections that have not been overcome appear in the paragraph below as they appear in the last Office action.

Response to Arguments

D). Applicants argue that a single chain antibody fragment and a scFv are not the same. An scFv is a "single chain molecule composed of two heavy and light chain variable regions fastened together by a flexible linker." Exhibit B was presented as support. Applicants further argue that a single chain antibody fragment is not limited to the variable regions only and thus can include more than the variable regions of the heavy and light chains in the single chain fragment.

In response, attention is directed to page 3, lines 29-31 which defines the single chain antibody fragment as scFv which is the same as the definition provided in Exhibit B and as well known in the art. Applicants have not presented any evidence of any single chain antibody fragment besides the known definition for scFv.

E). Applicants argue that claim 3 is not a duplicate of claim 1. Claim 1 is argued to require only the characterization of the bound antibody. Claim 3 includes the characterization of the unbound phage antibody as well as the bound phage antibody. In response, it is not clear as to the need of characterizing the unbound (washed out) phage antibody. This is especially true, as the specification does not recite a step or method by which the unbound phage antibody is characterized.

Claims 1 and 3, as amended, is indefinite as to the step of synthesizing a set of hterologous oligopeptides derived from the target protein. It is not clear in the manner a heterologous oligopeptides are derived from a target protein. Does it refer to the continuous or non-continuous, linear or secondary structure of a peptide sequence in one or more target protein?

Double Patenting

Claims 1, 3, 5-10 and 13-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims1, 5, 6 of U.S. Patent No. 6,265,150('150 patent) or claims 1, 5, and 6 of U.S. 2002/0132228('228 patent) in view of Middledorp et al for reasons set forth in the last Office action.

As a preliminary matter, as stated in the interview upon the availability of the Middledorp reference, the rejection would be reconsidered. [Note that Exhibit A is not on file.}

Response to Arguments

Applicants acknowledge that the claims of the '150 patent and the '228 patent are drawn to a method of obtaining phage antibodies directed to a cell surface antigen using whole cells. But argue that a person of ordinary skill in the art would not conclude that the use of whole cells is an obvious variation of the use of a set of heterologous oligopeptides in a method to identify phage antibodies that bind certain antigens. Whole cells differ from oligopeptides in size, charge, shape, and in some cases, binding affinity. Methods employing whole cells would require distinct binding conditions relative to methods employing oligopeptides. For example, buffers, temperature, incubation times, suitable detection methods, and assay set up are likely to be different.

In reply, the argued set of heterologous oligopeptides is nothing more than the fragments of the whole antigen. A whole cell antigen is known to contain antigenic determinant i.e., binding regions. The argued differences in the physical properties of the whole antigen vs. its fragments are obvious to

one having ordinary skill in the art to determine when a whole cell antigen or fragment is to be employed.

Applicants further argue that the intended purpose of the methods of the '150 patent and the '228 application are to identify antibodies, which bind cell surface antigens on intact cells. The use of glycopeptides to identify binding antibodies is not restricted to surface antigen as targets, and therefore represents a change in the principle of operation from the claimed methods of '150 patent and the '228 application.

In response, applicants' argument is unclear s to the oligopeptides binding not restricted to surface antigen as targets when the library are also antibodies i.e., the antibody-antigen reaction are the same in the instant as in the '150 patent and '228 application. Except the instant invention uses fragments of the whole antigens. The whole antigens as stated above are known to contain the set antigenic determinants or fragments that are responsible for specific binding to the antibodies and not the whole or entire antigen molecule. As applicants state at page 10, paragraph 2 of the instant REMARKS "...set of heterologous oligopeptides is..... known in the art...."

Applicants admit that Middeldorp employs the Geysen method to identify an immunodominant epitope of a target antigen. In other words, Middeldorp employs oligopeptides sets for use with

sera from antigen-reactive patients to identify the particular peptide that is immunodominant, i.e., bound by the antibodies of most individuals exposed to the target antigen. But argue that none of the cited references provide a method to simultaneously and specifically identify the bound oligopeptide and the bound polypeptide.

In response, applicants cannot show non-obviousness by attacking the references individually where the rejection is based on a combination of references. In re Young, 159 USPQ 725 (CCPA 1968). Middledorp is employed for the purpose of showing that synthesis of a set of oligopeptides derived from the region of a whole molecule is well known in the art, as recognized by applicants, supra.

Applicants admit that in the methods of '150 patent and '228 application, the antibody can be identified by isolating and growing out the phage antibody. But argue that this provides no indication of the identity of the peptide bound by the phage antibody.

In reply, it is considered that contact and binding have been determined before the antibody can be identified. In any antigen-antibody reaction, binding needs to occur and identify before that specific antibody that is known to bind to antigen

can be isolated. That is, the '150 and '228 has taken it further by identifying and isolating those antibodies that bound the antigen. See the claims of the '150 patent and '228 application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-10 and 13-18, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable de Kruif et al (J. Mol. Biol., 1995) in view of Geysen et al(Jrnl. of Immunological Methods) and Granoff et al (6,030,619).

De Kruif discloses, entire article, specifically the Discussion section at page 101 up to page 103, a method of identifying binding of scFv comprising constructing a library of phage display of scFv antibody fragments that displays scFv, contacting said phage display antibodies with a set of heterologous antigens such as human von willebrand factor (VWF A2) (page 103, col. 1). De Kruif at page 102, col. 1, paragraph

2 discloses that specificities of phage antibodies(Phabs) reaction is obtained by using portions of a molecule of e.g., the antigen A2 for selection. De Kruif does not disclose the use of oligopeptides (albeit set of heterologous antigen fragments is suggested) as claimed. Geysen discloses at page 160, col. 1 a systematic approach that uses complete sets of related peptides. Synthesizing peptides in this format results in numbers three orders of magnitude greater than conventional means. The conventional means can significantly affect the presentation of the peptide. Geysen disclose that the advantage of this systematic approach is that the number of negative controls incorporated into any experiment is very large, providing a statistical basis to set criteria for a significant positive interaction. At page 263, col. 1, the peptide synthesis is described. Furthermore, at page 264, RESULTS section, Geysen discloses that the epitopes i.e.,oligopeptides can be classified into two categories (1) sequential or continuous epitopes which consist of a linear sequence of amino acids homologous with the inducing antigen and (2) assemble epitopes where the site of antibody binding consist of amino acids distant in the linear sequence but brought together by folding (heterologous, as claimed).

Granoff discloses at col.9, lines 27 up to col. 10, line 17 the conventionality of the method of antigen-antibody binding or reaction using different antibody e.g., phage scfv and the different methods by which antigen that reacts with antibodies can be determined e.g., by Geysen method.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to employ in the method of de Kruif a set of heterologous oligopeptide as taught by Geysen. The numerous advantages taught by Geysen in the used of oligopeptides (i.e., epitope of the antigen) provides the motivation to one having ordinary skill in the art. This is especially true in light of de Kruif disclosure that a fragment of the whole antigen provides a specificity binding with the Phabs. Furthermore, as taught by Granoff this method is conventional in the art i.e., the used of phage scFv with sets of oligopeptides in solid support.

Claims 1, 3, 5-10 and 13-18, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable Burnie for reasons set forth in the last Office action.

Response to Arguments

Applicants submit that Burnie discloses a method using two separate steps to identify scFv phage antibodies specific for a target antigen. In the first step, the antigen is epitope mapped

using the Geysen method. Once the epitopes are defined using the sera, the epitope-encoding peptides, i.e., individual peptides, are used to pan the scFv phage antibodies in the second step. The scFv phage antibodies are never panned against a set of overlapping oligopeptides.

In reply, applicants' attention is drawn to the Burnie's abstract. Burnie recites that in the epitope mapping of the derived amino acid sequence, nine epitopes were delineated. At page 1601, column 2) Burnie discloses the panning of scFv against these nine epitopes but only two heterologous peptides(which can be considered a set) and a third peptide were selected to enrich scFv after panning. [It is of interest to note that the specification at page 17, lines 15-20 uses scFv preparations and not phage preparations.]

[Applicants' arguments with respect to Geysen is unclear since Geysen is not used in the rejection. As applicants admit Geysen involves constructing a series of overlapping peptides on pins. This method facilitates epitope mapping of an antigen using various immune and non-immune sera.]

The rejection of the claims under 35 U.S.C. 102(a) as being anticipated by Burnie et al is withdrawn in view of the 103 rejection, above.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0812. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
July 10, 2004